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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
UNGAR, SUSAN NMN	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 02/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/380,337	CHANDRASEKHARAPPA ET AL.	
	Examiner	Art Unit	
	Susan Ungar	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *24 November 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1,3-5,14-24,26,30 and 32-37* is/are pending in the application.

4a) Of the above claim(s) *14-18,34 and 35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1, 3-5, 19-24, 26, 30, 32, 33, 36, 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. The Amendment filed November 24, 2004 in response to the Office Action of May 19, 2004 is acknowledged and has been entered. Claims 3, 4, 19, 30 and 32 have been amended, Claims 2, 6-18, 25, 27-29, 31, 38-42 were previously canceled and claims 34-35 are withdrawn. Claims 1, 3-5, 19-24, 26, 30, 32-33, 36-37 are currently under prosecution.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. The following rejections are maintained:

Claim Rejections - 35 USC 112

4. Claims 1, 30, 32-33, 36-37 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper mailed March 19 2004 Section 5, page 3 and previously set forth in the paper mailed March 25, 2003, Section 4, page 2 drawn to claims 1-3, 5, 30, 32-33 and 36-37.

Applicant argues that (a) the specification teaches how to identify menin proteins with 95% identity to SEQ ID NO:2 by alignment programs and (b) teaches regions of the protein that are mutated in disease and the Examiner provides no evidence or reasoning as to why one of skill in the art would not be able to use such sequences, to raise antibodies to identify wild-type or mutant menin proteins and Applicant requests withdrawal of the rejection.

The argument has been considered but has not been found persuasive because (a') other than the possibility that the putative encoded polypeptide is a tumor suppressor, the specification provides no guidance as to the function of the encoded polypeptide, provides no guidance on how the encoded polypeptide acts as a tumor suppressor, provides no guidance on domains or amino acids critical to the function of the encoded polypeptide as a tumor suppressor, provides no

guidance on which of the 5% of amino acid residues of SEQ ID NO:2 can be altered without abolishing critical functions and thus provides no guidance on how to make the claimed invention. Further, given this lack of guidance in the specification, the ability to align the putative polypeptide sequence with other polypeptide sequences does not remedy the deficiency of the specification or provide guidance on how to use the encoded variant polypeptide in the absence of information drawn to the effects of the variation in amino acid sequence on protein function. The function of the encoded protein is in fact unknown and for the reasons of record one would not know how to make or use the claimed invention, (b') applicant is arguing limitations not recited in the claims as currently constituted. The claims as currently constituted are not drawn to isolated or recombinant nucleic acids encoding variant menin polypeptides which can raise antibodies that identify wildtype or mutant menin proteins and are not limited to the recombinant nucleic acids encoding the specifically mutated proteins disclosed in Example 1, Figure 3 and Figure 4.

The arguments have been considered but have not been found persuasive and the rejection is maintained.

5. Claims 1, 3-5, 19-24, 26, 30, 32-33, 36-37 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in the Paper mailed March 19 2004 Section 6, pages 3-6 and previously set forth in the paper mailed March 25, 2003, Section 5, pages 2-3.

Applicant argues that there is a nexus between the sequences of the instant application and those referred to by Wautot et al. Examiner has been convinced by Applicant's arguments and exhibits. However, given this nexus, as previously set forth, the findings of the Wautot et al reference are particularly relevant to this

rejection. Wautot et al specifically teach, on page 880, col 2 that "We did not detect any obvious alteration in menin expression levels and cellular location in LCLs carrying germ-line mutations compared with LCLs from none-affected individuals .....It appears that regulatory mechanisms maintain a constant level of expression, whether both alleles are functional or not." Further, Guru et al, 1999 specifically teaches, as previously set forth, that the amino acid sequence of 'this putative tumor suppressor offers no clue to the function... of the protein" (see abstract). Given this information, one would not know how to use the encoded protein or antibodies specific for the encoded protein. Since applicant has not distinctly and specifically pointed out the supposed errors in this ground of the instant rejection, the rejection is maintained.

6. Claims 3-4 and 32 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper mailed March 19 2004 Section 8, pages 8-9.

It is noted that the amendment of claim 3 to delete the terms non-coding' and "introns" and the amendment of claim 4 to be dependent upon claim 1 does not obviate the grounds of rejection because the chromosome clearly comprises the coding region of SEQ ID NO:1 and comprises SEQ ID NO:3.

Applicant argues that the specification contains extensive direction for using the claimed sequences, that is how to use the sequences in expression vectors and points to the section beginning on page 24. Further the specification teaches that the claimed polynucleotide can be used as a probe to evaluate MEN1 DNA in a nucleic acid sample. The fact that one or more nucleotides may be added to SEQ ID NO:3 does not negate the ability of a practitioner to make and use the claimed sequences.

The argument has been considered but has not been found persuasive because as previously set forth, the claims as currently constituted read on the entire chromosome for the reasons of record. The specification does not teach which other genes are located on the chromosome or how to use the other genes that are located on the chromosome. A review of the section beginning on page 24 reveals teachings drawn to the expression of the polypeptide as a recombinant protein with one or more additional polypeptide domains linked thereto and is drawn to an exemplary expression vector which provides for expression of a menin fusion protein comprising the encoded menin and nucleic acid encoding six histadine residues followed by thioredoxin wherein these residues facilitate detection and purification as well as an enterokinase cleavage site which provides a means for purifying the desired proteins from the remainder of the fusion proteins. However, the cited teachings do not teach how to express the menin protein in an expression vector comprising the chromosome on which the encoding polynucleotide is found, given that it would be expected that the stop codon found on the first protein encoding sequence on the chromosome would halt transcription and prevent the expression of menin protein and given that the specification does not teach how to direct protein expression specifically to the menin protein on the entire chromosome. Further, one would not be able to use the entire chromosome as a probe to evaluate MEN1 DNA in a nucleic acid sample because the probe would be expected to bind to and identify a multitude of nucleic acid molecules encoding a multitude of polypeptides and the specification does not teach how to use a probe that would be expected to bind to a plethora of polynucleotides encoding polypeptides other than SEQ ID NO:2 to predictably identify the

polynucleotide encoding SEQ ID NO:2. The arguments have been considered but have not been found persuasive and the rejection is maintained.

7. Claims 1, 30, 32-33, 36-37 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper mailed March 19, 2004 Section 10, pages 13-17.

Applicant argues that written description of a genus can be achieved by a precise definition, such as by structure, formula or chemical names and unlike *Lilly*, the instant specification recites a structural feature that is, that the claimed invention must have at least 95% identity to the reference sequence, SEQ ID NO:2. Further, like *Enzo*, the specification provides structural hallmarks by identifying in Example 1, Figure 3, and Figure 4, mutations identified in patients with multiple endocrine neoplasia type 1.

The argument have been considered but have not been found persuasive because the claims as currently constituted are not drawn to isolated or recombinant nucleic acids which are found to be mutated in patients, but rather are drawn to nucleic acids encoding variant menin polypeptides. Although the specification clearly discloses MEN1 polynucleotides that are mutated in patients with multiple endocrine neoplasia type 1 as compared to normal control, these mutated polynucleotides do not provide a representative number of isolated or recombinant polynucleotides encoding menin polypeptides with at least 95% identity to SEQ ID NO:2, which reads on a whole universe of molecules with alterations, mutations across the entire range of the encoded protein, which are other than the frameshift, nonsense, missense and in-frame deletion mutations disclosed in the specification. These mutations provide no guidance on how to predictably identify other members of the genus, in particular, because the

specification does not teach, as per *Lilly*, structural features common to the members of the genus which features constitute a substantial portion of the genus. This is critical given the information that the mutations found in the genes of the patients assayed included not only frameshift, but also nonsense, missense and in-frame deletion mutations.Further, the written description of the instant specification does not meet the standard of *Enzo*, the specification does not provide a correlation between the "structural hallmarks" and any function as required by *Enzo*.

The arguments have been considered but have not been found persuasive and the rejection is maintained.

8. Claims 19-24 and 26 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper mailed March 19, 2004 Section 11, pages 17-20.

Applicant argues that as stated above, the claims recite a structural hallmark, the reference sequence which provides identifying characteristics of the genus of nucleic acids encoding SEQ ID NO:2. The argument has been considered but has not been found persuasive because for the reasons set forth above, the recitation of SEQ ID NO;2 does not provide identifying characteristics of the genus of nucleic acids encoding SEQ ID NO:2 There is no information drawn to structural features common to the members of the genus which features constitute a substantial portion of the genus since the mutations in the gene described from various patients are drawn to not only frameshift but also to nonsense, missense and in-frame deletion mutations.

Applicant further argues that MPEP states that "in the molecular biology arts, if an applicant discloses an amino acid sequence, it would be unnecessary to

provide an explicit disclosure of nucleic acid sequences that encoded the amino acid sequence. Since the genetic code is widely known, a disclosure of an amino acid sequence would provide sufficient information such that one would accept that an applicant was in possession of the full genus of nucleic acid encoding a given amino acid sequence." Thus, human menin polymorphisms and allelic variants that encode SEQ ID NO:2 are acknowledged in the MPEP to be readily recognizable by those in the art and Applicants have satisfied the written description requirement.

The argument has been considered but has not been found persuasive because although the MPEP clearly teaches that given the teaching of an amino acid sequence, one would be in full possession of the genus of nucleic acid encoding a given amino acid sequence, the issue raised is not drawn to whether or not the specification provides a written description of the genus of polynucleotides encoding SEQ ID NO:2, rather the question raised is that the specification teaches only a single gene/cDNA that is mutated in multiple endocrine neoplasia-type 1 and that this is not sufficient to provide a written description of the broadly claimed polynucleotides that encode SEQ ID NO:2 that are also mutated or deleted so that one would be able to predictably identify those included in the genus claimed. Given only the single gene/cDNA, the specification does not provide a representative number of the claimed polynucleotides encoding SEQ ID NO:2 which constitute a substantial portion of the genus. Further, no functional characteristics coupled with a known or disclosed correlation between function and structure are provided.

The arguments have been considered but have not been found persuasive and the rejection is maintained.

Claim Rejections - 35 USC 102

9. Claims 1, 3-5, 30, 32-33, 36-37 remain rejected under 35 USC 112, first paragraph for the reasons previously set forth in Paper mailed March 19, 2004, Section 13, page 21.

Applicant argues that the '318 patent discloses extraction of genomic DNA from a hybrid cell line containing a deletion mutant of chromosome 11 and the chromosomes from the other species, hamster, are present. Thus, the "isolated" genomic DNA in fact comprises many, many chromosomal sequences, accordingly the genomic DNA from the hybrid cell line does not constitute an isolate nucleic acid as claimed in the instant invention.

The argument has been considered but has not been found persuasive because the specification clearly teaches that the term "isolated" as defined in the specification means that the molecule or composition is separate from at least one other compound, such as a protein, other nucleic acids, or other contaminants with which it is associated *in vivo* or in its naturally occurring state. Given this definition, the chromosome of the '318 patent clearly meets the limitations of the claims.

Applicant argues that the genomic DNA from the somatic cell hybrid was then cloned into a phage library. Examiner appears to be concerned that the library would inherently have a clone that comprises a MEN1 gene that encodes SEQ ID NO:2, however, there is no teaching that this genomic DNA library in fact contained a clone comprising any menin sequences or that a clone comprising a fragment encoding a full-length human menin was present in this library. The MPEP explains that when a reference is silent about an asserted inherent characteristic, extrinsic evidence may be provided to fill in the gap, however, such

evidence must make clear that the missing descriptive matter is necessarily present in the thing transcribed in the reference and that it would be so recognized by persons of ordinary skill. The examiner provides no such evidence.

The argument has been considered but has not been found persuasive because Examiner clearly pointed to CHO-K1 cell line which comprises the entire human chromosome 11 on a Chinese hamster background. Examiner never pointed to the library disclosed in the reference but specifically stated that US Patent No. 4,594,318 teaches isolated human chromosome 11..... a transfected cell comprising said chromosome, CHO-KI, which as defined by the specification is an expression vector. No extrinsic evidence is required to fill any gap since the expression vector comprises the entire chromosome. The arguments have been considered but have not been found persuasive and the rejection is maintained.

New Grounds of Rejection

10. Claim 30 is rejected under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 30 is confusing in the recitation of "A transfected cell *in vitro*". The claim is confusing because it is not clear whether the claim is drawn to a cell transfected *in vitro* or whether the claim is drawn to a cell that was transfected, for example, *in vivo* and is now found *in vitro*. The rejection can be obviated, for example, by amending the claim as suggested in the paper mailed March 19, 2004, page 13 to read "an isolated transfected cell".

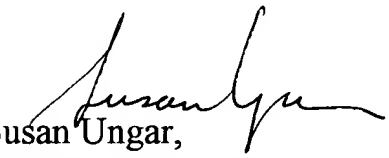
11. All other objections and rejections recited in the previous action are hereby withdrawn.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Susan Ungar, PhD whose telephone number is (571) 272-0837. The examiner can normally be reached on Monday through Friday from 7:30am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew, can be reached at (571) 308-0787. The fax phone number for this Art Unit is (571) 273-8300.



Susan Ungar,
Primary Patent Examiner
February 14, 2005